Cost-effectiveness of lurasidone vs aripiprazole among patients with schizophrenia who have previously failed on an atypical antipsychotic: an indirect comparison of outcomes from clinical trial data

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

CRD summary
This study assessed the cost-effectiveness of lurasidone, compared with aripiprazole, for treating adult patients with schizophrenia, who had failed to respond to generic atypical antipsychotics. The authors concluded that lurasidone was less costly and more effective than aripiprazole. The results and modelling were well reported, but given the uncertainty around the use of all the best evidence available, the authors’ conclusions may need to be interpreted with caution.

Type of economic evaluation
Cost-effectiveness analysis

Study objective
The objective was to assess the cost-effectiveness of lurasidone and aripiprazole for adult patients with schizophrenia, who had failed to respond to one or more of the generic atypical antipsychotics.

Interventions
Lurasidone was compared with aripiprazole. Both were atypical antipsychotic drugs, and standard treatments for schizophrenia in this setting. Generic therapy included olanzapine, risperidone, quetiapine and ziprasidone.

Location/setting
USA/secondary care.

Methods
Analytical approach:
A Markov cohort model was developed to simulate the treatment pathways over five years. When discontinuing either lurasidone or aripiprazole for any reason, patients were switched to clozapine and remained on this for the rest of the analysis. The transition probabilities for the Markov model were estimated using a multi-step indirect comparison of published studies. The authors stated that they took a third-party payer perspective.

Effectiveness data:
The annual transition probabilities for discontinuation (for any reason and lack of efficacy) and hospitalisation were derived from published studies, using a multi-step indirect comparison. The cardio-metabolic consequences of each treatment, which included weight change, cholesterol change and the relative risk of diabetes, were incorporated in the model. These data were from comparative clinical trials and a retrospective analysis. The annual risk of each cardio-metabolic factor was estimated using the Framingham 10-year cardiovascular risk profile and the Framingham body mass index (BMI) risk equation. The multi-step indirect comparison linked two studies of lurasidone with two studies of aripiprazole, using the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). CATIE was a randomised, double-blind study of four atypical antipsychotics (olanzapine, quetiapine, risperidone and ziprasidone) and one first-generation antipsychotic (perphenazine). The two lurasidone studies were a randomised, double-blind parallel-group comparison with quetiapine extended-release, and a double-blind, active-controlled trial comparison with risperidone. The two aripiprazole studies were a long-term maintenance comparison with oral haloperidol, and an open-label extension comparison with olanzapine.

Monetary benefit and utility valuations:
Measure of benefit:
The main benefit measure was hospitalisations avoided. The study also compared relapses, rates of diabetes, and rates of cardiovascular events. Outcomes were discounted at 3% per year.

Cost data:
The cost categories were drugs, mental health care, diabetes management, and cardiovascular events. Annual drug costs were estimated based on their wholesale prices from the Red Book, and mean doses from published studies. Psychiatric care for patients with and without a relapse, were from published literature. The costs of diabetes management were from published literature. The annual costs of a cardiovascular event were estimated based on a large administrative claims analysis. Costs were inflated to 2012 US$, using the Medical Care Component of the Consumer Price Index of the Bureau of Labor Statistics, and discounted at an annual rate of 3%.

Analysis of uncertainty:
One-way sensitivity analysis was conducted on several model parameters, using the 95% confidence intervals as a proxy for high and low values. Several scenario analyses were undertaken: the lipid Framingham risk equation was used instead of the Framingham BMI risk equation; the discount rate was varied; and the costs were varied. Probabilistic sensitivity analysis was undertaken and the results were presented as cost-effectiveness acceptability curves.

Results
The total cost for aripiprazole was estimated at $90,500. The total cost for lurasidone was $86,480. Lurasidone was estimated to have fewer relapses per patient, fewer hospitalisations per patient, a lower rate of diabetes per patient, and lower rates of cardiovascular events per patient, compared with aripiprazole.

Lurasidone was more effective and less costly than aripiprazole, when assessing the cost per hospitalisation avoided and the cost per relapse avoided.

Sensitivity analysis found that the results were generally robust. Only one scenario affected the results; when mental health costs were excluded, lurasidone no longer dominated (was more effective and less costly than) aripiprazole. This resulted in an incremental cost-effectiveness ratio of $12,180 per hospitalisation avoided or $42,447 per relapse avoided.

The probabilistic sensitivity analysis estimated that, at a willingness-to-pay threshold of $50,000 per hospitalisation avoided, lurasidone had a 100% likelihood of being more cost-effective than aripiprazole, and at the same threshold per relapse avoided, lurasidone had a 99.3% likelihood of being more cost-effective.

Authors' conclusions
The authors concluded that lurasidone could be a less costly and more effective treatment than aripiprazole for adult patients with schizophrenia. Investigations of the cost-effectiveness of lurasidone in real-life settings were needed.

CRD commentary
Interventions:
The interventions were briefly described. It was not clear why aripiprazole was chosen as the comparator nor why clozapine was chosen as the third-line treatment. Standard care, beyond the generic atypical antipsychotics, was not discussed, so it was unclear if the comparators reflected usual practice.

Effectiveness/benefits:
The trials included in the indirect comparison were not described sufficiently to allow their validity to be assessed, but the suggestion was that they had high internal validity. No systematic review was reported to ensure that all the best available evidence was included. This was particularly important, given that an a multi-step indirect comparison was required for the two interventions. Few details of the indirect comparison were presented, it was unclear which software was used and which statistical techniques were undertaken, so the reliability of the analysis is unclear. It appears that it would have been possible to conduct the indirect comparison using risperidone instead of quetiapine; there were direct trials for lurasidone versus risperidone as well as quetiapine, and both drugs were included in the CATIE trial. No
justification for choosing quetiapine was included. Using both comparisons could have verified the results, given the lack of direct comparisons.

**Costs:**
The costs seem to have been appropriate for the perspective chosen, and they were derived from appropriate sources. Only some of the resource use estimates were described, which reduces the ability to reproduce these estimates for another setting. The costs were appropriately discounted and adjusted for inflation.

**Analysis and results:**
The economic model was adequately described, and a simple diagram of its structure was presented. As stated earlier, no justification was provided for using clozapine as the third-line treatment, but this may have been widely acceptable. The results were clearly presented and the sensitivity analysis was comprehensive. The authors highlighted the increased uncertainty around the multi-step indirect comparison, compared with a simple indirect comparison, and the variation between the patient populations in the trials.

**Concluding remarks:**
The results and modelling were well reported. The lack of description of the indirect analysis and the selection of trials for that analysis increased the uncertainty, but the extensive sensitivity analysis suggested that the results were robust. Given the uncertainty in the use of all the best evidence available, the authors' conclusions may need to be interpreted with caution.

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